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Determinants of Mortality for Necrotizing Soft-Tissue Infections

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Objective

The authors determined the risk factors of mortality in patients with necrotizing soft-tissue infections (NSTIs) and examined the incidence and mortality from NSTI secondary to *Streptococcus pyogenes*.

Methods

All patients with NSTIs who were treated between January 1989 and June 1994 were analyzed for presentation, etiology, factors important in pathogenesis and treatment, and mortality.

Results

Sixty-five patients were identified with NSTIs secondary to postoperative wound complications (18), trauma (15), cutaneous disease (15), idiopathic causes (10), perirectal abscesses (3), strangulated hernias (2), and subcutaneous injections (2). Necrotizing soft-tissue infections were polymicrobial in 45 patients (69%). *S. pyogenes* was isolated in only 17% of the NSTIs, but accounted for 53% of monomicrobial infections. Eight of ten idiopathic infections were caused by a single bacterium ($p = 0.0005$), whereas 82% of postoperative infections were polymicrobial.

An average of 3.3 operative debridements per patient and amputation in 12 patients were necessary to control infection. The overall mortality was 29%; mortality from *S. pyogenes* infection was only 18%. The average time from admission to operation was 90 hours in nonsurvivors *versus* 25 hours in survivors ($p = 0.0002$). Other risk factors previously associated with the development of NSTIs did not affect mortality.

Conclusions

Early debridement of NSTI was associated with a significant decrease in mortality. *S. pyogenes* infection was the most common cause of monomicrobial NSTI, but was not associated with an increased mortality.

Necrotizing soft-tissue infections (NSTIs) comprise a spectrum of disease entities that are characterized by extensive, rapidly progressive soft-tissue necrosis that usually involves the muscular fascia and subcutaneous tissue, but can also affect the skin and muscle. Necrotizing soft-tissue infections are classified as cellulitis, fasciitis, or myositis, based on the principal soft-tissue layer involved with necrosis.[1] These infections can have either an indolent or fulminant presentation, and their clinical course is unpredictable.[2] Joseph Jones, a surgeon in the Confederate Army, wrote one of the earliest descriptions of NSTIs and reported a mortality rate of 46% in 2642 soldiers afflicted during the Civil War.[2–4] Subsequent mortality rates from NSTIs have varied from 6% to 76% (Table 1).[2–31] Individual factors that have been implicated to increase mortality from NSTI include increasing

age; obesity; diabetes mellitus, peripheral vascular disease, and other systemic diseases; malnutrition; anatomic sites of infection involving the trunk; delay in surgical debridement; a higher Acute Physiology score and a higher Surgical Infection Stratification score.[4,6-9,11,14,24,29] Unfortunately, the small number of patients reported in most series of NSTIs has precluded definitive identification of risk factors for mortality.

Meleney[5] presented his original description of "hemolytic streptococcal gangrene" in 1924, reporting a 20% mortality rate in 20 patients with fulminant NSTIs. Beta-hemolytic streptococcus was the causative organism isolated from all of these soft-tissue infections. Wilson in 1952[2] and Crosthwait and colleagues in 1964[5] found that *Streptococcus pyogenes* was the cause of 58% and 57% of necrotizing fascial infections, respectively. Subsequent reports have documented a decline in the incidence of NSTI caused by β-hemolytic streptococci, which was consistent with a general decline in incidence of all serious streptococcal infections that were noted in the United States throughout the 20th century.[4,9,14,23,28,32] In more recent years, it has been suggested that the frequency of severe Group A streptococcal infections is increasing. Stevens et al.[32] has reported a resurgence of severe NSTI secondary to *S. pyogenes*, with an associated increase in mortality. This changing pattern of serious hemolytic streptococcal soft-tissue infection has been postulated to result from an increase in the virulence of Group A streptococci.[32]

The purpose of the present study was to evaluate risk factors for mortality in a large group of patients with NSTI from a single institution and to examine the current incidence and mortality of NSTI secondary to *S. pyogenes*. Delays in recognition and treatment and parameters that may indicate more advanced disease were associated with a poor outcome.

Table 1. REPORTED MORTALITY RATES FROM NECROTIZING SOFT-TISSUE INFECTIONS

Authors	Year	No. of Cases	No. of Mortalities	Percent
Meleney[5]	1924	20	5	20
Wilson[2]	1952	23	2	9
Crosthwait et al.[6]	1964	19	6	31
Rea and Wyrick[7]	1970	44	13	30
Stone and Martin[8]	1972	63	48	76
Ledingham and Tehrani[9]	1975	20	11	55
Casali[10]	1980	12	4	33
Kaiser and Cerra[11]	1981	20	8	40
Freeman et al.[12]	1981	14	4	29
Oh et al.[13]	1982	28	10	36
Rouse et al.[14]	1982	27	20	73
Majeski and Alexander[15]	1983	30	10	33
Walker and Hall[16]	1983	8	3	38
Miller[17]	1983	15	4	27
Adenolfi et al.[18]	1983	11	3	27
Spirnak et al.[19]	1984	20	9	45
Stamenkovic and Lew[20]	1984	19	8	42
Barzilai et al.[21]	1985	11	1	36
Pesa and Howard[4]	1985	33	11	33
Freischlag et al.[22]	1985	21	11	35
Gozal et al.[23]	1986	16	2	12
Sudarsky et al.[24]	1987	33	2	6
Clayton et al.[25]	1990	57	10	18
Asfar et al.[26]	1991	10	3	30
Ward and Walsh[27]	1991	14	6	43
Wang and Shih[28]	1992	18	6	33
Francis et al.[29]	1993	25	6	24
Chow et al.[30]	1993	12	3	25
Brown et al.[31]	1994	54	19	35
Cumulative		696	239	34
Present series		65	19	29

METHODS

A retrospective review was completed of all patients with NSTI involving the subcutaneous tissue and fascia with or without associated skin or muscle necrosis who were treated at MetroHealth Medical Center between January 1989 and June 1994. Patients were identified from a computer-generated ICD-9 search through the Medical Records Department. Patients with primary clostridial and nonclostridial myonecrosis were excluded. Necrotizing soft-tissue infection was defined by the presence of necrosis of the subcutaneous tissue and fascia, with variable involvement of the skin and muscle. The presence of necrosis was confirmed from results of frozen or permanent histopathologic tissue examination in all patients.

Medical records were reviewed for the following: age; gender; etiology of bacterial inoculation; factors thought to predispose to the spread of infection including obesity, diabetes mellitus, peripheral vascular disease, intravenous drug abuse, alcoholism, hypoalbuminemia, and corticosteroid use; comorbid illnesses; anatomic site of infection; clinical manifestations of infection; laboratory findings; time from hospital admission to operation; percent body surface area involved; bacteriology; number of operative debridements; need for amputation; and mortality.

The anatomic site of infection was classified as either trunk, extremity, or head and neck. Postoperative NSTI

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was defined as an NSTI that occurred in a recent operative incision. Time from hospital admission to surgery was not applicable in this group of patients; thus, they were not included in this determination. Leukocytosis was defined as a white blood cell count >10,000/μL, acidosis as a pH < 7.35, hypocalcemia as a corrected calcium <8.4 mg/dL, and anemia as a hemoglobin level <10 mg/dL.

Data from direct chart review were entered into a microcomputer database using CSS Statistica (Stat Soft, Tulsa, OK). Continuous data were analyzed using a Student's t test and discrete data were analyzed using a Fishers' exact comparison. A p value of <0.05 was considered significant.

RESULTS

Sixty-five patients were treated for NSTI, including 51 with necrotizing fasciitis, 12 with necrotizing fasciitis and associated myonecrosis, and 2 patients with necrosis confined to the skin and subcutaneous tissue. There were 33 men and 32 women ranging in age from 15 to 87 years with a mean age of 50 years. The etiology of NSTI was postoperative necrotizing fasciitis in 18 patients (28%), soft-tissue trauma in 15 (23%), cutaneous infections or ulcers in 15 (23%), idiopathic infections in 10 (15%), perirectal abscesses in 3 (5%), strangulated hernias in 2 (3%), and subcutaneous injections in 2 (3%). Postoperative NSTI occurred after contaminated operations in 17 patients and a clean-contaminated operation in 1 patient. Soft-tissue injury was due to blunt trauma in nine patients, penetrating trauma in three patients, and miscellaneous causes in three patients. Factors predisposing to the spread of infection included obesity in 30 patients, diabetes mellitus in 29, hypoalbuminemia in 26, peripheral vascular disease in 17, chronic alcoholism in 8, corticosteroid use in 7, and intravenous drug abuse in 5. Forty-nine patients (75%) had between one and five serious comorbid illnesses (mean = two).

The principal anatomic site of infection was the trunk in 37 patients, the extremities in 26, and the head and neck in 2. Clinical manifestations of NSTI included soft-tissue edema in 49 patients (75%), erythema in 47 (72%), severe pain in 47 (72%), tenderness in 44 (68%), temperature > 38 C in 39 (60%), and skin blebs, bullae, or necrosis in 25 (38%). Pain at the site of infection was absent or considered to be minor in 18 patients; 9 of these patients had postoperative NSTI, 5 had altered mental status, 3 had diminished sensation secondary to diabetic neuropathy or paraplegia, and 1 patient had a perirectal abscess. Laboratory findings included leukocytosis in 46 patients (71%) (mean white blood cell count = 16,300), anemia in 25 (38%), hypocalcemia in 14 (22%), and acidosis in 11 (17%). Soft-tissue gas was present in 19 patients (29%), 8 of whom had crepitation on physical examination and 11 of whom had soft-tissue gas detected on radiographic imaging studies consisting of either plain roentgenograms in five patients, computed tomography in four patients, or both studies in two patients.

Table 2. CAUSATIVE ORGANISMS FOR 45 POLYMICROBIC NSTIs (n = 127)

Aerobes (gram-positive)	51 (40%)
Enterococci	21
Streptococcal species*	11
Coagulase negative staphylococci	10
Staphylococcus aureus	6
Bacillus species	3
Aerobes (gram-negative)	54 (43%)
Escherichia coli	15
Pseudomonas aeruginosa	13
Enterobacter cloacae	5
Klebsiella species	5
Proteus species	4
Serratia species	4
Acinetobacter calcoaceticus	3
Others†	4
Anaerobes	19 (15%)
Bacteroides species	12
Clostridium species	4
Others‡	5
Fungi§	3 (2%)

* Includes Group B streptococcus (3), gamma streptococcus (non faecalis) (3), alpha streptococcus (2), *S. milleri* (1), and *S. pyogenes* (2).
† Includes *Citrobacter freundi* (2), *Xanthomonas maltophilia* (1), *Eikinella corrodens* (1), and *Aeromonas hydrophilia* (1).
‡ Includes Peptostreptococcus (2) and diptheroids (1).
§ Includes *Candida tropicalis* (2) and *Candida albicans* (1).

All patients were treated with immediate operative debridement, broad spectrum parenteral antibiotics, and repeated operative debridements and amputation as necessary to control infection. Three patients with NSTI of the perineum underwent diverting colostomy, and all patients with postoperative NSTIs had abdominal wall reconstruction using polypropylene mesh. Information about the time interval from hospital admission to operation was available for 40 patients (mean 45 hours, range 1.7–312 hours). The average time from admission to operation was 90 hours in nonsurvivors *versus* 25 hours in survivors (p = 0.0002). The percent body surface area involved by NSTI varied from 0.5% to 12% (mean 5%). An average of 3.3 intraoperative debridements were performed per patient (range 1–22), and 12 patients required lower extremity amputation for control of infection. Patients who required amputation had a higher incidence of peripheral vascular disease (75% *vs.* 15%, p = .0001) and diabetes mellitus (66% *vs.* 38%, p = 0.11).

The microbiology of NSTIs was polymicrobial in 45 patients (69%) (Table 2) and monomicrobial in 19 pa-

Table 3. CAUSATIVE ORGANISMS FOR THE 19 MONOMICROBIC NSTIs

Streptococcus pyogenes	10
Clostridium perfringens	2
Staphylococcus aureus	2
Pseudomonas aeruginosa	1
Escherichia coli	1
Serratia marscesans	1
Gamma-*streptococcus*, not enterococcus	1
Candida glabrata	1

tients (29%) (Table 3); no organisms grew from intraoperative culture in 1 patient. The number of organisms isolated in each patient varied from one to four species. Patients with polymicrobial infections had an average of 2.8 organisms isolated from their infections. The predominant organisms in polymicrobial infections were gram-negative enteric bacilli, enterococci, and staphylococcal and streptococcal species. Twenty percent of patients had cultures that grew a combination of aerobic and anaerobic bacteria. Postoperative infections were polymicrobial in 82% of patients ($p = 0.07$). Ten of 19 monomicrobial infections were caused by *S. pyogenes* (53%) (Table 3). *S. pyogenes* was isolated from only two patients with polymicrobial infection. Necrotizing soft-tissue infections secondary to *S. pyogenes* were more likely to be monomicrobial ($p = 0.00003$), idiopathic ($p = 0.001$), painful ($p = 0.027$), and involve the extremities ($p = 0.05$).

Nineteen patients (29%) died. Early mortality, which was defined as death within the first 10 days after the initial debridement, occurred in six patients, all as a result of overwhelming sepsis. Three of these patients developed acute renal failure, two had adult respiratory distress syndrome, one had mesenteric ischemia, and one had both a urinary tract infection and aspiration pneumonitis. Thirteen patients died more than 10 days after the first debridement (mean 53 days, range 16–247 days). Late deaths occurred due to multi-organ system failure in 11 patients, myocardial infarction in 1 patient, and an arrhythmia in 1 patient. All patients had failure of one to three organ systems, including respiratory failure in 11, hepatic failure in 5, renal insufficiency in 5, cardiac failure in 3, mesenteric ischemia or gastrointestinal hemorrhage in 3, bone marrow failure in 1, and adrenal insufficiency in 1.

Of the 12 patients with NSTI secondary to *S. pyogenes*, either alone[10] or in combination with other bacteria,[2] only 2 died. This mortality rate was not significantly different from NSTI caused by other bacteria ($p = 0.48$). Gender, etiology of infection, obesity, diabetes mellitus, alcoholism, intravenous drug use, hypoalbuminemia, corticosteroid use, anatomic site of infection, presence of soft-tissue gas, bacteriology, and associated myonecrosis did not significantly impact on outcome. Factors that had a statistically significant impact on outcome in patients with NSTIs and those factors that approached statistical significance are listed in Table 4.

DISCUSSION

The 29% mortality rate in this series compares favorably with other reports of patients with NSTI. The cumulative mortality rate of nearly 700 patients with NSTI is 34% (Table 1). The mortality from NSTI in the current series occurred in two distinct time periods. Early deaths accounted for 32% of overall mortality and were due to the consequences of sepsis and septic shock. These patients had more virulent courses, and although local infection was controlled, these patients died rapidly from systemic manifestations of infection. Late deaths occurred after a more protracted hospital course and were characterized by progressive organ system failure. Stone et al.[8] reported that 63% of the deaths from NSTI occurred within 7 days of hospital admission, and Rouse et al.[14] found that 45% of the deaths from NSTI occurred within 10 days of initial debridement and resulted from either persistent infection after inadequate debridement or rapidly progressive septicemia. In the series reported by Ledingham and Tehrani,[9] early mortality occurred in only 2 of 11 patients with fatal infections, and these deaths resulted from causes unrelated to the underlying infection. More recently, Clayton et al.[25] reported 10 deaths in 57 patients with perineal NSTI, all of which occurred 10 to 95 days after debridement.

The most common etiology of NSTI in our series was postoperative necrotizing fasciitis, which primarily occurred after operations with extensive fecal contamination. Minor skin infections and soft-tissue trauma were

Table 4. RELATIONSHIP BETWEEN CLINICAL CHARACTERISTICS AND MORTALITY IN PATIENTS WITH NECROTIZING SOFT-TISSUE INFECTIONS

Variable	Survived (n = 46)	Died (n = 19)	p Value
Time from admission to operation (hrs)	25 ± 39	90 ± 95	0.0002
Percent body surface area involvement	4.7 ± 3.0	6.4 ± 3.4	0.054
Acidosis (n = 11)	5	6	0.057
Peripheral vascular disease (n = 17)	9	8	0.071
No. of comorbid illnesses	1.5 ± 1.2	2.2 ± 1.6	0.073
Age (yrs)	48 ± 14	56 ± 21	0.076

other common causes for NSTI, and both were causes for limb loss and death. Idiopathic NSTI, an entity that has previously been reported to account for approximately 20% of NSTIs,[33] occurred in 15% of our patients. The particular etiology of NSTI was not demonstrated to have a significant impact on outcome.

The microbiology of NSTIs in the current series was characterized by a wide variety of organisms cultured from affected wounds (Tables 2 and 3). As was true in an earlier review of the bacteriology of necrotizing fasciitis,[34] streptococci and the Enterobacteriaceae were the most common bacteria isolated. The current group of patients had a much higher incidence of infection involving enterococci, which had been reported previously by Rouse and colleagues[14] and likely reflects a high incidence of postoperative NSTI. We also had a higher incidence of infections caused by *Pseudomonas aeruginosa* compared with other series.[14,31,34] The incidence of polymicrobial infections in our series is similar to the results of Guiliano and colleagues,[34] who found that 81% of patients had synergistic infections. Only 25% of our patients had anaerobic bacteria cultured from sites of infections. This differs from previous studies, which have demonstrated that anaerobic organisms are isolated in 61% to 89% of patients and comprise 25% to 42% of all organisms isolated.[14,25,28,31,34] Possible explanations for this disparity include failure to obtain anaerobic cultures, delayed or improper processing of cultures, and imprecise isolation and culture techniques.

Statistical analysis of the potential determinants for mortality from NSTI demonstrated that only a prolonged time from hospital admission to operative debridement was associated with an unfavorable outcome. This confirms previous reports which have emphasized that delayed debridement of NSTI is associated with increased morbidity and mortality.[4,8,15] Patients who had systemic acidosis or a larger percentage of body surface area involved with necrosis were more likely to die from NSTI, although this parameter did not quite reach statistical significance. Both of these characteristics seem to be associated with advanced disease and more fulminant infections; however, they also may reflect delays in seeking medical evaluation, which could not be accurately quantified. Increasing age, the presence of peripheral vascular disease, and a greater number of comorbid illnesses were other factors that approached statistical significance in the patients who died from NSTI (Table 4). Other authors have emphasized the lethal nature of NSTI in the elderly and in patients with chronic debilitating or immunosuppressive conditions.[4,6–8,14] Risk factors that had previously been associated with an increased mortality in patients with NSTI, such as diabetes mellitus, malnutrition, and a truncal site of infection, did not have a significant effect on outcome in the current group of patients. These data strongly suggest that the primary impact physicians can have on mortality from NSTI is to recognize this malady earlier in its course to reduce the delay to operative debridement.

Necrotizing soft-tissue infection associated with *S. pyogenes* was more likely to be monomicrobial, painful, and involve the extremities. This organism was the principal cause of monomicrobial NSTI in our series, although it was cultured in only 17% of the patient population overall. The presence of *S. pyogenes,* alone or in combination with other bacteria, was not associated with an increased mortality. In fact, the mortality rate was similar to the 20% mortality rate reported by Meleney[5] before the introduction of antibiotics. These data suggest that the frequency, virulence, and mortality of NSTI secondary to *S. pyogenes* does not appear to be increased at our institution and that the mortality from NSTIs is not dependent on the species type or number of bacteria present.

Because of the demonstrated impact of early recognition and debridement of NSTIs, our practice is to advocate soft-tissue and fascial exploration with biopsy and frozen section examination, if necessary, to establish or exclude NSTI whenever the diagnosis is suspected, but not accompanied by associated clinical findings. Patients should receive empiric broad spectrum antibiotics, which should be effective against a wide variety of organisms commonly present in these infections. Single antibiotic choices would include imipenem-cilastin, ticarcillin-clavulanate, ampicillin-sulbactam, and piperacillin-tazobactam. Multiple drug therapy may be selected because of allergies, suspected antimicrobial resistance, or physician choice. Both aerobic and anaerobic cultures of the involved tissues are best obtained at the beginning of the operation. Antimicrobial therapy should be modified based on culture results and antimicrobial susceptibility testing.

Other therapeutic measures include adequate fluid resuscitation, correction of systemic acidosis and electrolyte abnormalities, and packed red blood cell transfusion, as necessary, to correct anemia which may occur as a result of toxin-induced intravascular hemolysis. Intravenous calcium gluconate was used to correct hypocalcemia, which occurred in 22% of patients. This abnormality is thought to occur secondary to calcium precipitation in areas of extensive fat necrosis.[7]

Routine re-examination of the area of infection should be performed within 24 hours to ensure that all infected and necrotic tissue has been debrided. This can be done either on the ward with the use of ketamine anesthesia or in the operating room. Repeated operative debridement should be performed until the infection is controlled. Amputation was required to control infection in nearly 50% of patients with extremity infections who were

noted to have a significantly higher incidence of underlying peripheral vascular disease compared with the remaining patients. A diverting colostomy often is needed to control infection in patients with perineal NSTIs.

After debridements, these wounds should be managed by frequent inspection and dressing with physiologic saline solutions. Parenteral narcotic analgesics are used for pain control. Early and adequate nutritional support, along with prompt recognition and treatment of nosocomial infections, have been shown to reduce the development of organ system failure and improve outcome.[14,15] No patient in our series was treated with hyperbaric oxygen. To date, the efficacy of hyperbaric oxygen in treatment of NSTIs has not been established by controlled studies, and delays in debridement have been reported with its use.[4]

These results indicate that prompt recognition and early debridement of NSTI can potentially improve the outcome of this serious disease. The extent of infection and the presence of acidosis indicate more virulent infections. Many other parameters previously reported to impact mortality from NSTI did not affect outcome in this group of patients.

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Discussion

DR. HIRAM C. POLK, JR. (Louisville, Kentucky): Dr. Williams, Dr. Copeland, Ladies, and Gentlemen. This is one paper you ought to read because I suspect you're going to see more of this.

First of all, this is really a good paper, but the thing about it is that with the growing numbers of barriers that are being erected between surgeons and their patients, you're going to see more of the worst kind of these. There's going to be more delay involved. And if there is any message to be taken home from this paper, aside from the fact that 1) it's very well done, 2) it's the largest series probably in the world, and 3) in the manuscript,